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The Treatment in Pneumococcic Pneumonia with Large Doses of Repository Penicillin Compared with Lower Doses of Penicillin: In an effort further to reduce the mortality rate among patients with pneumococcic pneumonia treated with penicillin, the authors undertook a study to compare the results that could be obtained from the use of large repository doses of penicillin with those obtained from the dosages generally in use.

Accordingly, 600,000 units of penicillin in oil and beeswax were administered twice a day to 238 patients, and 600,000 units of procaine penicillin in oil were given twice a day to 45 patients, with typed pneumococcic pneumonia. These 283 patients were designated as the "large-dose group." Other dosage forms of penicillin which produce lower blood concentrations were used in 403 patients who were designated as the "small-dose group." Among the latter, 236 were treated with intramuscular injections of penicillin at 3-hour intervals. In most cases, each dose was 15,000 units, but in occasional instances, it was 25,000, 50,000, or 100,000 units. Oral penicillin was given to 99 patients in doses of 80,000 or 100,000 units every 3 hours. Sixty-eight patients were given 300,000 units of procaine penicillin in oil with aluminum monostearate intramuscularly. Four of these patients received 2 injections 2 or 3 days apart. The remainder were given a single dose.

At least one specimen of sputum and blood was obtained from each patient for culture and typing. One or more roentgenograms of the chest were made. If, upon the basis of the history, physical examination, and roentgenograms, the patient was thought to have pneumonia and a type of pneumococcus was obtained from the sputum or blood, the patient was included among the patients herein reported.

The patients in the large-dose group were treated in the past 2 years, whereas those in the small-dose group were treated over the past 4 years. Other than this, no selection was practiced. The patients on an entire ward were given one or the other preparation of penicillin for several months without any alteration.

The proportion of patients affected by each type of pneumococcus was approximately the same in each of the 2 treatment groups. The case fatality rates in the 2 groups (5 percent in the large-dose repository penicillin group and 5.4 percent among the patients treated with smaller doses of penicillin) were practically identical. Bacteremia was present in 46 patients (16 percent) in the large-dose group and in 59 patients (14 percent) in the small-dose group. The fatality rates for the bacteremic patients in the 2 groups were very similar (13 percent and 10.2 percent).

The age distribution of the patients in the 2 groups was quite similar. Forty-seven percent of the patients in the large-dose group were over 40 years of age and the fatality rate in this group was 8 percent. In the small-dose group

43 percent of the patients were over 40 years of age. The fatality rate in this group was 10 percent.

The incidence of diseases associated with the pneumonia was approximately the same in the 2 treatment groups. Death occurred as frequently among the patients in the large-dose group with complicating diseases as in the small-dose group. The complications arising from the pneumonia were present to approximately the same degree in both groups. Death occurred in one patient with empyema in the small-dose group and in one patient with empyema and one patient with pleural effusion in the large-dose group.

It was found that the fatality rate in the large-dose group was almost the same as that obtained in patients treated with the more common penicillin dosage-regimens and the difference observed was not statistically significant. In the search for an explanation of these unexpected findings, two possibilities appear likely. The most obvious explanation is that the case fatality rate in pneumococcic pneumonia has been lowered to an irreducible minimum beyond which it cannot go because of factors upon which the antibiotics cannot operate. Among 14 patients who died after treatment with 600,000 units of repository penicillin at 12-hour intervals, 10 were over 40 years of age. Of these, 2 were admitted with acute alcoholism and pneumonia, 3 had hemiplegia and developed pneumonia as a complication, 2 had heart disease, 1 had cirrhosis of the liver, and 1 had prostatic hypertrophy, renal lithiasis and uremia. The 1 patient without an associated disease was a 42-year-old colored woman who was admitted on the 7th day of the disease and who had pneumococcic arthritis as well as pneumonia on admission.

Among the 4 patients who were below 41 years of age, 1 was admitted with acute alcoholism and pneumonia, 1 had rheumatic heart disease upon which a bacterial endocarditis had been engrafted before admission, and 1 had pneumococcal endocarditis, arthritis, and meningitis on admission. The 4th patient, who had no associated disease, was admitted moribund and died a few hours after a single dose of 600,000 units of penicillin in oil and beeswax.

Among the 18 patients in the small-dose series who were 41 years of age and over and who died, 7 had congestive heart failure, 2 had hemiplegia and 1 each had acute alcoholism, essential hypertension, uremia and purulent bronchitis with lung abscess. Four patients died within 24 hours after the first dose of penicillin had been administered. Of the remaining 2 patients, 1 was 80 years old and the other was a 63-year-old man with hypertension and diabetes mellitus.

Four patients died among the patients under 41 years of age in the small-dose group. One had congestive heart failure and chronic glomerulonephritis with uremia. One had diabetic acidosis. The 2 remaining patients died 8 and 15 hours after the first dose of penicillin was administered.

It may be of significance that 7 patients in the low-dose group died within 24 hours of admission, whereas only one patient in the repository penicillin group died during this period, although this difference may have been caused merely by the fact that a larger number of moribund patients were included in the low-dose group. The question under consideration is whether any of the patients who died could have been saved by the employment of any dosage of penicillin, however large. Even if an increased dose of penicillin would have resulted in 1 or 2 fewer deaths, the difference could not be demonstrated even by the finest of statistical methods, unless a much larger number of patients had been included in each series.

Another possible explanation of the results obtained is that the large doses of repository penicillin which were used, although assuring minimal penicillin concentrations, in practically every case, of 0.08 unit per cc., actually did not produce very high peak concentrations such as would have been attained with 1,000,000 units of penicillin, for instance. There are a number of proponents of the theory that high-peak concentrations of penicillin in the blood are more important than constant levels. If this theory is entertained, it would seem reasonable to try large doses of aqueous penicillin at infrequent intervals in pneumococcic pneumonia to determine whether the fatality rate could be depressed below 5 percent. (Am. J. M. Sc., July '50, H. F. Dowling et al.)

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Evolution of Neurologic Signs of Early Anterior Poliomyelitis: The data from which descriptions of the neurologic signs of early poliomyelitis have been derived have been obtained chiefly from occasional irregularly spaced examinations of large numbers of patients, each at some different time from the onset of the disease. It was thought that a more accurate description would result from frequent regularly spaced examinations both day and night during the early stage of poliomyelitis.

Accordingly, 11 neurologists were rotated in tours of duty of 6 hours during the day and night for 30 days in the Municipal Contagious Disease Hospital (Chicago). Frequent examinations of each patient were made from the time of entrance to the hospital following the diagnosis or presumption of acute anterior poliomyelitis. This resulted in the examination of a pool of patients - at first, the few who were admitted on the first day and this number increased by subsequent admissions. During the period of 30 days the pool was diminished by the discharge of patients at the end of their quarantine period to other hospitals or home. From the pool also were removed patients who may have died or in whom a bulbar type of poliomyelitis developed predominantly.

Excluding patients whose death or life in a respirator afforded a relatively short period of observation, the authors had available 30 patients for sufficiently long periods of study to permit of an analysis. Group A consisted of 16 patients

in whom the weakness developed to a degree classified as 0, 1, and 2, with 0 indicating total paralysis, 1, a flicker of movement, and 2, movement with gravity eliminated. Group B consisted of 14 patients in whom the muscles were graded 5, indicating normal strength, 4, indicating weakness against moderate resistance, and 3, indicating movement against gravity. For certain studies an additional 12 patients of the so-called meningitic type were included.

The time constant of the examinations was obtained by estimating the number of hours after the first sign or symptom which indicated the beginning of the disease. The decision so to time the examination was brought about by the fact that the time of invasion of the nervous system could not be determined accurately. In group A the succeeding examinations were made from 6 to 197 hours after the first sign or symptom, with a median of 106 hours. In group B the time ranged from 3 to 300 hours, with a median of 94 hours.

The frequent examinations resulted in the accumulation of large numbers of observations on many muscles in which paralysis, direct myotatic irritability, spasm, tenderness, or stretch pain was studied. There were also numerous examinations of many different deep and superficial reflexes and many observations of the Kernig, Lasègue, and Brudzinski signs and of rigidity of the spine. These observations also resulted in data which could with validity be used to show the changes in relation to time.

Thus, in seeking for spasm, tenderness, and stretch pain on which the authors have already reported, in the 30 cases a total of 670 muscle groups were examined, and the total number of muscle group examinations was 9,114. It may be restated that no muscle spasm was found during the time of development of paralysis in patients with acute anterior poliomyelitis, and tenderness and stretch pain occurred infrequently and only after paralysis had occurred.

Rigidity of the Spine, Kernig, Lasègue, Brudzinski Signs. Common to most infectious diseases of the central nervous system and to basal subarachnoid hemorrhage are the signs of rigidity of the neck and spine and the Kernig and Brudzinski signs. There is no general agreement concerning the altered physiology of these signs. Recently, authors have attributed signs in the neck and spine to abnormal reflex activity, with possibly uninhibited reflexes from labyrinthine stimuli and those from the reticular formation acting on antigravity muscles. Concerning the Brudzinski sign, particularly the direct, uninhibited neck and labyrinthine reflexes also have been invoked to explain it, because the flexion of upper and lower limbs on anteflexion of the head is found to occur in decerebrate animals. No experimental observation offers an adequate analogy for the Kernig sign.

Although in early anterior poliomyelitis all these signs may be elicited, in many instances they differ in degree and form from the same signs in meningitis. In meningitis, rigidity of the neck is found in all cases. In 277

competent observations in the authors' cases of anterior poliomyelitis, it likewise was fairly constant, appearing in 92.4 percent. However, in meningitis it is apparent from the beginning of the patient's attempt to flex the head; in fact, the head is often retracted. In the authors' cases, in only 9 percent was it found at 0 degrees from the horizontal. In the next 30 degrees of anteflexion, resistance was encountered in 43 percent of cases and from 30 to 60 degrees of anteflexion resistance was present in 32 percent.

In meningitis, the direct Brudzinski sign is present in all cases and requires but little flexion for its elicitation. Of 271 observations, the sign was present in only 37 percent. If cases ending with paralysis of the lower extremities are excluded, it was present in 44 percent. In only 4 percent was it produced from the beginning of movement; in 13 percent it appeared with flexion of the neck from 0 to 30 degrees; in 20 percent it appeared with flexion from 30 to 60 degrees. In contrast to meningitis, movement of the upper extremities rarely occurred.

In meningitis, the Kernig sign is constantly present. In the authors' cases it was present in 39 percent of 613 examinations. It occurred in only 3 percent in extension of the leg on the thigh to 45 degrees, in 10 percent to 90 degrees, and in 26 percent from 90 to 135 degrees. Fewer positive signs were found in extremities destined to be severely paralyzed.

The question arises concerning whether these heretofore described signs may be related to the presence of an upper motor neuron lesion. In known clinical entities there is evidence to the contrary. In comparing the rigidity of the neck and spine to bilateral cerebral lesions producing obvious evidence of upper motor neuron disorder, it may be said that in all it is the extremities which show spasticity, postural signs, reflex hyperactivity, and pathologic reflexes rather than the neck and spine. This holds for cortical lesions, as in cerebral palsy of childhood, and subcortical lesions producing cerebral diplegia and pseudobulbar palsy. In lesions of the extrapyramidal system, such as parkinsonism and the amyostatic syndrome of Strumpell, the neck and spine are somewhat rigid but in the opposite direction, namely flexion.

The Lasegue sign was found in about 50 percent of the 163 examinations up to the 100th hour; from then to the 150th hour it occurred in 72 percent of 127 examinations, and from then to the 200th hour it was demonstrated in 87 percent of 128 examinations. Although the Kernig sign did not continue to increase as time lengthened, it was present in 17 percent of the examinations up to the 100th hour and in 54 percent thereafter. The progression of these signs suggests that in early anterior poliomyelitis they result rather from a protective mechanism related to pain than from any upper motor neuron disease. The authors also believe that the rigidity of the spine is related to pain.

Onset and Progression of Paralysis. Usually premonitory preparalytic symptoms of the stage of invasion are present for from 1 to 7 days, rarely longer. However, this stage has been known to be as long as 21 days.

Armstrong noted paralysis in 70 percent of patients by the 3d day and in 95 percent by the 5th day. Paralysis often appeared suddenly, but it might be preceded immediately by a weakness which could be demonstrated only by the patient's inability to bear his weight. When permitted to walk, some patients showed ataxia. The initial paralysis, as observed in the majority of cases, proved to be the final extent. Spiller felt that the paralysis, preceded by weakness, required several days for its full development, but rarely was it progressive over more than 2 weeks. Wickman said it was very seldom complete at the beginning, usually increasing rapidly in extent and severity. Colliver has noted of these cases with spreading paralysis that when the paralysis has remained the same for a number of hours it spreads no more. In any case, it was believed that once improvement began, there was no further increase of paralysis. After reaching its height, the paralysis was said to recede. As a rule, the distal muscles recovered first and the upper extremity before the lower.

In obtaining the data for the study of paralysis, there were 470 examinations of all the principal prime movers of both sides. In analyzing the evolution of paralysis, 3,192 muscle examinations were made on those patients finally becoming severely paretic (of the order of 0-1-2) and 5,922 muscle examinations were made on muscles becoming only weak (of the order of 3-4) or normal. In some cases, some degree of weakness was noted as early as 6 hours after onset and severe paralysis as early as 18 hours after onset. In other cases, more and more muscles became weaker and weaker until the peak of total weakness of all muscles was reached at the 144th hour after onset. The peak of weakness of the various muscles was not reached immediately, but was preceded by varying degrees of weakness until the peak of a degree of 0-1-2 was reached. This peak occurred in practically all 16 patients in this group between the 75th and the 150th hour, and in only 2 did it occur under 50 hours.

Once weakness occurred, it did not regularly progress to the peak of paralysis of that muscle in all cases. The weakness increased, at times diminished, again increased, and then continued either to increase or partly to disappear. This variability from hour to hour was the striking observation in this study. In about two thirds of these cases, once the peak of 0-1-2 was reached the muscle strength remained in that level through the remaining time of observation. However, in a third of the cases, it often improved and finally became worse, or became better, then fluctuated and finally was better. The initial paralysis often was not of the same degree as that at the termination of observation in many cases. This early paralysis followed by various fluctuations was observed in a number of cases. It does not always hold true that when paralysis has remained the same for a number of hours it spreads no further. It is not true that once improvement occurs there is no further increase in paralysis; in about one fifth of the muscles studied improvement most certainly had occurred and the muscle finally became quite weak or paralyzed.

Reflex Changes in Anterior Poliomyelitis. Müller and Wickman have called attention to an initial increase in the deep reflexes in the preparalytic stage. The hyperreflexia may extend into the paralytic stage most frequently in those persons in whom paralysis is slight. It is also seen in the legs when only the arms are involved, in patients in whom spastic paralysis appears as the result of an involvement of the pyramidal tract,and in patients with meningitis. Weisenburg likewise noted exaggerated deep reflexes, as did many others. Regan and Armstrong noted diminution of these reflexes just preceding paralysis.

Persistence of a deep reflex during the paralytic stage is rare. When found, it indicates a rapid recovery or involvement of the pyramidal tract. Ankle clonus is also rare. Regan said it was often simulated in painful cases, which is likewise true of the false Kernig sign. He also said that the plantar reflexes are exaggerated in the preparalytic stage, accompanied by withdrawal of the entire leg. A Babinski sign has been noted in the preparalytic stage and usually is said to indicate a meningitic form of the disease.

It has been said that absence of deep reflexes is the rule. They may be normal in patients with the bulbar form of the disease. When only one leg is paralyzed, the other knee jerk may be normal, and if only the arms are paralyzed the knee jerks may at times be present but rarely exaggerated. Even if only the facial muscles are paralyzed, the knee jerks may be absent.

In this study, when muscles were destined to become severely or completely paralyzed,their deep reflexes were absent in 91 percent of 520 examinations. When the deep reflexes of a muscle group disappeared before the 50th hour after onset of illness, 41 percent of the cases terminated in complete paralysis. If the deep reflexes disappeared in from 50 to 75 hours, 50 percent terminated in severe paralysis; when from 75 to 100 hours, in 38 percent; when from 100 to 125 hours, in 28 percent. When the deep reflexes disappeared only after 125 hours, in none did weakness greater than Lovett's grade 4 develop. The earlier the deep reflexes disappear, the more likely it is that the muscle group will become paretic.

There was found as great a fluctuation in the state of deep reflexes in relation to time as in paralysis; that is, reflexes might disappear, reappear and again disappear. When a long period of hours of continued absence of a deep reflex finally ensued, then if the continued absence began soon after the first observation that a reflex was absent, complete paralysis occurred in over 60 percent of muscles. As time lengthened for the continuous absence of deep reflexes, the strength of the muscles did not diminish to the same degree as in the cases with earlier continued loss of a reflex. When no continued loss of deep reflexes was observed, then at the end of the period of observation no paralysis ensued in over 80 percent of muscles. In patients with some muscles which became severely paralyzed and other muscles which developed weakness,

but no residual paralysis, there was no loss of a deep reflex subserved by the latter muscles in 164 examinations up to 100 hours and in only 6 percent of the 51 examinations between 100 and 130 hours. They were found absent in only 3.1 percent of 291 examinations up to the 200th hour and were found increased in 57 percent.

Relation of the Abdominal Reflexes to Paralysis of the Extremities. In patients in whom severe paralysis of the lower extremities was destined to develop, it was found that the abdominal reflexes had disappeared in 85 percent by the 100th hour. When the severe paralysis involved only the upper extremities, the abdominal reflexes were absent in only 14 percent. When there was only weakness of the lower extremities, it was found that the abdominal reflexes had disappeared in 7.1 percent and with paralysis in neither an upper nor a lower extremity they had disappeared in 1.5 percent.

In the other group of patients, in whom none of the muscles of the extremities were destined to become paretic, the abdominal reflexes were absent in only 3.2 percent of 340 examinations of the 4 abdominal reflexes, and they were increased in 57 percent. A further study of the hyperactivity of the abdominal reflexes revealed that when only the upper extremities were destined to become severely paralyzed the reflexes were increased in 42 percent of 328 examinations. When only the lower extremities were destined to become paralyzed, the abdominal reflexes were never increased.

Relation of the Plantar Reflex to Paralysis of the Extremities. In none of these cases was there paralysis of the flexors of the toes. The plantar reflex was never absent when only the upper extremities were paretic, or when neither upper nor lower extremities were paretic. Moreover, when the lower extremities were severely paretic, the plantar reflexes did not disappear and remain absent but rather disappeared, reappeared, and fluctuated throughout. They were absent, however, at various times in 35 percent of 179 examinations of severely paretic lower extremities, and in 2.3 percent of 128 examinations when moderate weakness in the lower extremities occurred. The reflexes were brisk in 25 percent of the patients with severely paretic lower extremities, in 64.5 percent of those with moderate weakness, in 85 percent of those in whom only the upper extremities were affected, and in 64 percent of those in whom no muscle was paretic.

The Babinski sign was found at one or another time in 28 of 481 examinations of patients. It was found in all groups. When there was severe paralysis of the lower extremities, it was present in 6.1 percent of 179 examinations; it was present in 11 percent when there was paralysis only of the upper extremities, and in 6.4 percent when no paralysis occurred. It was found irrespective of whether the deep reflexes were absent or increased. Such fleeting, inconstant, and unrelated instances may well be compared to its appearance in anesthesia after epileptiform attacks and anoxia.

It has been suggested that signs of upper motor neuron involvement may be masked by destruction of anterior horn cells. That such could be the case can be seen from amyotrophic lateral sclerosis, in which increased deep reflexes of the upper extremity may diminish and finally disappear when the destruction of anterior horn cells becomes severe enough.

It is well known that in upper motor neuron lesions, when the deep reflexes are hyperactive, the abdominal reflexes are either absent or diminished and a Babinski sign is fairly constant. It was thought that a study of such relations might contribute to further elucidation of whether the patients had involvement of the upper motor neuron. The authors' findings showed that when muscles were destined not to become paretic, the deep reflexes were hyperactive in 57 percent, and at the same time the abdominal reflexes were absent in but 2 percent of the examinations, while the plantar reflexes were hyperactive in ercent. Furthermore, in this group the Babinski sign was found in only 6.4 percent. When the lower extremities were severely paralyzed and the deep reflexes absent in 91 percent of examinations, the abdominal reflexes were also sent in 97 percent. When only the upper extremities were to become paralyzed, the plantar reflexes were hyperactive in 85 percent of examinations, whereas the abdominal reflexes were hyperactive in 42 percent.

Thus it is seen that there was no correlation between the hyperactive deep reflexes and the diminution of superficial ones. Also, occurrence of the Babinski sign is rare and was unrelated to the state of the deep reflexes; therefore, it is believed that in these cases of early anterior poliomyelitis there was no evidence to show that lesions of the upper motor neuron were constant or even common.

Relation of Direct Myotatic Irritability to Paralysis. After injury to a peripheral nerve, the muscles which it supplies become hyperirritable to electric and mechanical stimuli during the stage of denervation. It was thought to be of interest to study the response of muscles to direct mechanical percussion during early anterior poliomyelitis.

Direct myotatic irritability was found to be increased predominantly in muscles of the upper extremities when they were paralyzed, as compared with those of the lower extremities. It was increased in 40 percent of 295 observations on the upper extremities and 5 percent of 365 observations on the lower extremities when the observations were made at various times during the period of hospitalization. Direct myotatic irritability was found to be increased in a greater percentage of paralyzed than unparalyzed muscles of the upper extremities. Thus, of 295 observations on paralyzed muscles, in 40 percent it was increased, whereas in 691 observations on unparalyzed muscles it was increased in 17 percent. Nevertheless, in many instances when a muscle was completely paralyzed, for example, from the 120th to the 270th hour after onset,

direct myotatic irritability may not have been increased. In general, the increase of direct myotatic irritability was more related to the time after onset than to the degree of paralysis. It seemed to be increased when paralysis occurred soon after onset, whereas, despite complete paralysis of a muscle after, for example, the 160th hour after onset, it may not have been found to be increased. On the other hand, in some it was increased many hours after a muscle became completely paralyzed.

In general, myotatic irritability decreased after longer periods, so that after the 250th hour nc increase was found in either paralyzed or unparalyzed muscle, although the numbers of observations at this late time were smaller than in the preceding hours.

Increased direct myotatic irritability not only was inconstant in appearance but fluctuated to a great degree in the successive observations on each patient during the time of hospitalization. This may be illustrated from an analysis of all of the cases. Between 40 and 50 hours, direct myotatic irritability was increased in 100 percent of the muscles examined, between the 190th and 210th hours it was increased in none, and between the 230th and 240th hours it was again found to be increased in 100 percent. The failure to find a constant correlation between the development of paralysis and other signs of denervation in the muscles was reflected also by studies on the response of such muscles to electric stimuli. Despite complete paralysis, the rheobase did not fall to the small values observed in injuries of peripheral nerves nor did the galvanic tetanus ratio fall to 1.0. In this respect, the paralysis in anterior poliomyelitis acted much as did that related to injuries of the cauda equina or brachial plexus, in which sufficient numbers of nerves reached the muscle to neurotize it to such a degree that evidence of complete denervation could not be obtained, and still the total number of intact fibers was insufficient to produce the energy necessary for voluntary motion. (Am. J. Dis. Child., June '50, L. J. Pollock et al.)

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Absorption and Excretion of Terramycin Compared with Aureomycin and Chloramphenicol: Terramycin is a recently discovered antimicrobial compound (Medical News Letters of 24 February 1950 and 19 May 1950) which has been found to be active against a number of bacterial species in vitro and to suppress experimental infections in mice. Studies in laboratory animals have indicated that terramycin, like aureomycin and chloramphenicol, is well absorbed following oral administration. It seemed desirable, therefore, to make a study of the absorption, distribution, and excretion of terramycin following its administration to human beings and to compare the data with those obtained following the administration of aureomycin or chloramphenicol. In addition, the serum concentrations of these drugs attained in patients under treatment with various dosage regimens have been determined.

Terramycin was supplied as the amphoteric base in 250 mg. capsules and 2.5 Gm. vials for aqueous suspension and as the hydrochloride in 250 mg. capsules and compressed tablets. Aureomycin hydrochloride was available in 250 mg. capsules and in 50 mg. vials. Chloramphenicol was provided in 250 mg. capsules.

The determinations of absorption and excretion of aureomycin and chloramphenicol following a single oral dose of drug were made in the same subjects. All subjects were fasted for 12 hours preceding the ingestion of a single large dose of drug. Blood specimens were drawn with sterile precautions at intervals after the drug administration. The urine was likewise collected at intervals during the 8- or 24-hour period following the ingestion of drug, all specimens were pooled, and aliquots were sterilized by Seitz filtration prior to assay.

Specimens of serum and other body fluids were collected at random from patients receiving daily maintenance doses of these drugs. Simultaneous withdrawals of blood and cerebrospinal fluid were made from a number of patients who had been given a single large dose of drug several hours before lumbar puncture or from patients receiving maintenance doses. All serum, urine, spinal fluid, and other specimens were kept frozen until time of assay.

Microbiologic assay was carried out both with a 2-fold serial dilution technic and a modification thereof which provided fractional dilutions of the unknown. The test organisms used in the assay procedures were Bacillus cereus and Streptococcus hemolyticus, C203Mv.

Although studies of the concentrations of an antimicrobial drug which are attained in the blood may bear only a very loose relationship to the therapeutic results which will be achieved with the administration of that drug, the results of such studies can nevertheless be valuable in serving as a guide to the dosage regimens to be employed in therapy, and in comparing the absorption and excretion of various forms of the same drug. It was found that all 3 drugs were readily absorbed after oral administration. Of the 3 compounds studied, chloramphenicol provided the most rapid accumulation of antimicrobial substance in the serum and yielded the highest serum concentrations. The maximum serum concentrations attained after oral doses of 50 mg. per kilo were from 25 to 50 µg. per ml for chloramphenicol, from 12 to 16 µg. per ml for terramycin, and from 3.3 to 12.5 µg. per ml for aureomycin. Concentrations of terramycin in the serum were obtained following single large doses or with daily maintenance doses of terramycin hydrochloride which were similar in magnitude to those concentrations attained with equivalent doses of aureomycin given by mouth. The persistence of measurable serum concentrations of terramycin for periods of 6 hours and longer after single doses, and the high serum concentrations attained when from 1 to 1.25 Gm. maintenance doses of drug were given at 6-hour intervals, indicate that total daily doses of from 4 to 5 Gm. by mouth will provide satisfactory drug concentrations in the body in terms of the in vitro sensitivities of the various microorganisms against which terramycin has been demonstrated to be effective.

Measurable concentrations of the compounds were obtained in the cerebrospinal fluid and in other body fluids when sufficiently large doses of the drugs had been administered. Of the 3 drugs, chloramphenicol accumulated in the cerebrospinal fluid to the greatest extent. Urinary excretion of the 3 substances in biologically active form was similar, and high concentrations of drug were attained in the urine. (Proc. Soc. Exper. Biol. and Med., June '50, C. A. Werner et al.)

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Acute and Subacute Glomerulonephritis Modified by Adrenocorticotropin: The data compromising this preliminary report were collected for the purpose of investigating the acute or subacute phases of glomerulonephritis under the influence of adrenocorticotropin. Attention was directed less toward phenomena associated with water and electrolyte metabolism than those associated with inflammation and with azotemia. In view of the transitory character of acute glomerulonephritis in children, with or without therapy of any sort, patients were selected in whom the disease was of long duration.

The first patient was a 12-year-old girl who had been treated for subacute glomerulonephritis and rheumatic heart disease for 6 weeks. Gross hematuria, azotemia, and hypertension had been present throughout that period. When she was admitted to the hospital, the urine was claret-colored and the 24-hour output contained an average of 7 Gm. of protein. There was a loud apical systolic murmur; the blood pressure was 152/110 and the blood urea was 54 mg. per 100 cc. The erythrocyte count was 3,500,000 and the hemoglobin was 6.7 Gm. Because there was no evidence of edema, she was given a general diet, without salt restriction. She was started on small doses of ACTH, totalling 27 mg. daily, Armour standard. Even at this dose, the blood pressure rose abruptly, and after the 4th day the medication was discontinued for 2 days. With the reinstitution of ACTH, the blood pressure appeared to be favorably affected, and the total dose was raised to 50 mg. daily. Notwithstanding the fluctuations of pressure, the hematuria diminished after the 2nd day of treatment, and by the 5th day, the urine was straw-colored. Microscopic examination of the centrifuged passed specimen, several days later, showed only an occasional erythrocyte. Daily injections of ACTH, 25 mg., were given to the patient for the month following discharge from the hospital. Follow-up studies performed 8 months after treatment showed a normal blood pressure and absence of blood in the urine, but a slight increase in the blood urea and nonprotein nitrogen.

The 2nd patient was a 9-year-old girl who was admitted to the hospital with a history of rheumatic heart disease and subacute glomerulonephritis of 5 months' duration. The systolic blood pressure ranged from 176 to 188, the diastolic from 90 to 110. There was a loud systolic murmur, best heard at the

apex, and a marked pulsus alternans. The erythrocyte count was 2,970,000, the hemoglobin 7.7 Gm., the leucocyte count 7,150. The urine was grossly bloody and contained 3.4 Gm. of protein in 24 hours. The blood urea nitrogen was 73 mg., the nonprotein nitrogen 144 mg., the serum cholesterol 361 mg., creatinine 3.0 mg., total protein 5.5 Gm., and albumin 2.9 Gm. After four days of control studies, ACTH was administered in doses of 20 mg. every 4 hours. By the 5th day of treatment the urine was straw-colored and microscopic examination of the morning specimen showed only an occasional erythrocyte. The diastolic blood pressure averaged 22 mm. lower during this interval than during the control period. Adrenocorticotropin was then discontinued for the subsequent 5 days, at the end of which the urine had again turned dark red and the centrifuged specimen was found to be packed with erythrocytes. A 2nd course of ACTH was also associated with the disappearance of red cells. This patient was studied for 35 days, with varying doses of ACTH. Upon discharge from the hospital the blood urea nitrogen was 42 mg., the creatine 1.8 mg., and the serum cholesterol 205 mg. Follow-up studies 7 weeks after discharge indicate that the diastolic blood pressure remained below 90 mm.; the nonprotein nitrogen was found to be 44 mg. per 100 cc.; the erythrocyte count was 4,080,000, and the hemoglobin 10.5 Gm. Hematuria redeveloped soon after the patient returned home, and has remained present in varying degree.

The 3d patient was a 5-year-old girl who was hospitalized with acute glomerulonephritis of several weeks' duration. Edema had been present on admission but had subsided soon after. The blood urea nitrogen was moderately elevated. The urine was smoky and loaded with erythrocytes. The volume was small and the concentration of protein was high. This patient was given 10 mg. of ACTH every 6 hours. The eosinophils disappeared from the circulating blood, and by the 5th day the smoky urine turned straw-colored. The blood urea nitrogen fell from 28 to 15 mg. per 100 cc., rose to 22 mg. percent after 10 days of withdrawal, and returned to normal when medication was again started. Because of the relatively short duration of the disease in this patient, less significance is attributed to the abatement after administration of ACTH.

It is concluded that hematuria, azotemia, and hypertension associated with the active phases of glomerulonephritis can be favorably modified by activation of the adrenal cortex with ACTH. (Proc. Soc. Exper. Biol. and Med., May '50, E. B. Farnsworth)

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Reduction of Mortality in Mice from X-Radiation by Treatment with Antibiotics: In a preceding study, the results of blood and spleen cultures on mice subjected to a single exposure of 600 or 450 roentgen units total body x-radiation showed an incidence of bacteremia which rose and fell during the 2nd post-irradiation week roughly parallel with the daily death rate. This finding suggested

that infection might be a significant factor in death from radiation injury. An attempt, therefore, was made to reduce the mortality from x-radiation by controlling the bacteremia by the administration of antibiotics. Because the bacteremia was found to be caused by microörganisms (mostly Gram-negative bacilli) normally inhabiting the lower intestinal tract of these mice, it was concluded that to be effective an antibiotic must be active against a wide variety of bacterial species.

Male Swiss mice were exposed to a single dose of 450 r x-radiation delivered at 20 kv., 15 ma., at a distance of 27 in., using 1/2-mm. copper and 3-mm. bakelite filter. The dose rate was approximately 20 r per min. Their LD_{50} (30 days) was about 400 r. After irradiation, they were divided into control and treated groups, so that each therapeutic trial contained a group of control mice that had received the same dose of irradiation on the same day. From the 4th to the 28th day after irradiation, the treated mice were injected subcutaneously with 0.5 ml of saline containing antibiotic. Control mice received daily injections of 0.5 ml saline subcutaneously for the same period of time.

The results show that streptomycin administered subcutaneously once a day from the 4th through the 28th day after irradiation significantly reduced the mortality during the 30-day period of observation. In the group treated with 6,000 ug. of streptomycin, 16 percent died, as compared with 81 percent of the controls. Doses of 5,000 and 7,000 ug. of streptomycin showed less striking but still significant degrees of protection. The group treated with a combination of 5,000 ug. of streptomycin and 10,000 units of penicillin had a 30-day mortality of 25 percent, compared with 66 percent for the controls.

Preliminary trials with other antibiotics have shown chloramphenicol to be somewhat less effective than streptomycin alone or in combination with penicillin. Chloramphenicol, as well as aureomycin, caused a considerable degree of irritation at the site of the injection. In some of the mice there was even necrosis of the skin. These deleterious effects are being obviated in current experiments in which the drug is administered in food. Polymyxin B in doses of 0.2, 0.1, 0.05, and 0.02 mg. failed to reduce the mortality. In fact, the death rate was increased by the larger dose, presumably because of its toxicity. Results with aureomycin were irregular. One experiment showed a significant reduction in mortality but another experiment showed none, probably because infection with a strain of Pseudomonas aeruginosa insensitive to aureomycin appeared among the mice in that group.

It seems, therefore, that, to be effective in reducing mortality from irradiation injury in mice, a chemotherapeutic agent must provide protection against infections by bacteria normally present in the animal, and also against all pathogens which might establish themselves within its body during the period when the animal's natural resistance to infection is markedly reduced. Among

the antibiotics tested, streptomycin has provided the most effective protection. (Science, 30 June '50, C. P. Miller et al.)

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Long-Term Follow-Up Study of Penicillin-Treated Subacute Bacterial Endocarditis: This is a report on the altered clinical pattern seen in patients with subacute bacterial endocarditis since the advent of penicillin therapy, and the effect of this therapy on long-term results. From 1944 through 1947, a period arbitrarily chosen to provide at least a one-year follow-up study on the most recent cases, 60 patients with proved subacute bacterial endocarditis were admitted to Peter Bent Brigham Hospital. Diagnosis was substantiated by 2 positive blood cultures, the association of two or more classic clinical signs with at least one positive blood culture, or postmortem examination. Patients were selected for study who had received 200,000 units or more of penicillin a day for at least 10 days and who either were followed for over a year after therapy or came to autopsy. Thirty-eight patients met these criteria. Two of the 38 patients were retreated for reinfection, 15 and 16 months, respectively, after bacteriologic cure of the initial infection. During the interim, both were followed and were noted to be free of the stigmas of the smoldering or "bacteria-free" stage of bacterial endocarditis. Thus 40 episodes of treated subacute bacterial endocarditis in 38 patients were analyzed in this study.

The average age at onset for the group was 34 years; 20 were females, and 18 males; 83 percent had pre-existing rheumatic valvular disease. Among the congenital defects present in 6 patients, there were 5 cases of patent ductus arteriosus, 1 of interventricular septal defect, and 1 of a bicuspid aortic valve. Dental extractions or major fillings without associated penicillin prophylaxis had been carried out in 38 percent of the patients within the immediate weeks before the development of endocarditis. Upper respiratory infections, furunculosis, pyelitis, appendicitis, and cystitis preceded endocarditis in 6 other patients, whereas in 20 patients no antecedent infection could be implicated. The alpha-hemolytic streptococcus was the responsible organism in 33 of the 40 episodes. There were 2 cases of double infection, one with Alcaligenes faecalis which developed during penicillin treatment and one with Escherichia coli. These organisms were isolated both from the blood during life and from the heart valves at autopsy in each of these patients.

The average duration of infection, as indicated by onset of symptoms before admission, was 3-1/2 months, with a range extending from 2 days to 1 year. Symptoms of infection were noted by all but 1 patient. Ninety-three percent had a history of a murmur before infection developed, and in all the murmur remained essentially unchanged during the hospital stay. Sixty-four percent of the patients who subsequently survived had a fever on admission, and all but 1 of those in the fatal cases were febrile at that time. Nine of the 12 patients who

died had symptoms of congestive failure before the start of treatment, whereas such symptoms were present in only 3 of the 28 who recovered. Arthralgia, splenomegaly, and embolic phenomena were slightly more common among the fatal cases. The presence of albumin in the urine, with red cells and casts in the sediment, was more common among those who subsequently did not survive.

Fourteen patients were tested intracutaneously, before and after treatment, with a protein derived from beta-hemolytic streptococci. All had negative tests before therapy. Nine patients who subsequently survived, and 3 others, who at autopsy showed no evidence of active infection, had a positive test after therapy. Two patients, however, whose tests remained negative after therapy did show actively infected valves at autopsy.

To some extent weight loss and the degree of anemia depended upon duration of infection before admission. Although the erythrocyte sedimentation rate was elevated in most patients on admission, the rate did not always fall with successful treatment.

When this series was first begun in 1944, penicillin therapy consisted of 200,000 units given intravenously for 14 days. Duration of treatment was soon extended to 3 and then 5 weeks or longer, depending on the clinical response. At present, 2,000,000 units or more is given daily in divided doses intramuscularly every 3 hours, with the use of combined sodium and procaine penicillin in the latter weeks of therapy. Cure has resulted from as little as 200,000 units daily for 2 weeks or as much as 4,000,000 units daily for 6 weeks, but no one treatment schedule has been uniformly successful. Four patients with persistent fever and bacteremia received in stepwise fashion increased amounts of penicillin. Three of them responded satisfactorily within from 2 to 4 days to the change in treatment. Despite changing therapeutic practices, a relatively stable year-to-year penicillin cure rate has been observed, with an over-all result of 28 cures in 40 episodes, or 70 percent. The paradox of a stable annual cure rate in the face of increased treatment schedules may be explained on the basis that only the patients with the more refractory cases of subacute bacterial endocarditis were sent to the hospital in the last few years.

Of 28 cured patients, 26 showed a fall in temperature and pulse rate within from 5 to 10 days. In contrast, 11 of 12 patients subsequently dying of the disease showed no fall in temperature with treatment. Other clinical and laboratory evidences of healing were slower to appear. Encouraging signs, however, were clearing of the urinary sediment, disappearance of the anemia, return of the sedimentation rate to normal, and disappearance of splenomegaly.

Before the advent of effective treatment, the diagnosis was often made by the eventual development of obvious signs. Now, however, early diagnosis is of practical importance, and one must suspect bacterial endocarditis in some

patients even in the absence of classic signs. On admission, fully a quarter of the patients in this series did not show an anemia, a fever, or abnormal urinary findings.

Congestive failure developing during the time of untreated infection was one of the most ominous prognostic signs. Seventy-seven percent of the patients with failure died during the course of the disease. In general, a more rapidly developing clinical picture presaged a poor outcome. Once treatment was initiated, failure of the temperature and pulse to fall within from 2 to 4 days on increasing amounts of penicillin, failure of clinical and laboratory signs to recede and, particularly, failure of the skin test for streptococcus to revert to positive indicated a grave prognosis, even though blood cultures were negative and the initially isolated organism sensitive to penicillin in vitro. Age, sex, duration of infection, underlying disease, and predisposing causes did not appear to influence the prognosis. In this series no organisms except the two Gram-negative bacilli were resistant in vitro to penicillin, and yet at autopsy two thirds of the patients who died showed actively infected valves. A similar finding has been reported by other observers.

The incidence of congestive failure was 38 percent of the patients in this series at some time, and 27 percent of 511 cases collected from the literature. In most cases congestive failure was believed to be caused by a combination of myocardial lesions and valvular destruction. As pointed out by others, neither the degree of valvulitis nor the presence of myocarditis has been consistently associated with the presence of cardiac failure. The findings in this study, although not conclusive, are compatible with this view, and support the concept that multiple factors are concerned in the production of failure in this disease. The presence of active bacterial endocarditis in 7 patients who died with cardiac failure, despite penicillin therapy, and the peculiar downhill course, once congestive failure had developed, suggest that a major change in the immune and tissue response of the host had occurred, allowing for the persistence of an ordinarily penicillin-sensitive organism. It is suggested that the development or progression of congestive failure, as a reflection of diffuse myocardial and valvular damage in many patients, may serve as a clinical indicator of such an alteration in the immunologic response.

Aschoff bodies were observed in the myocardium of 3 of the 13 patients who died during or shortly after treatment. Although the number of cases of proved rheumatic carditis was small, carditis was probably significant in the production of progressive failure seen in 2 patients, in neither of whom were the valve lesions striking. Opinion is as varied on the relation of rheumatic carditis to the development of failure in this disease, as it is on the causal or coincidental relation of active rheumatism to the development of endocarditis itself.

In the pre-penicillin era, clinical renal insufficiency was present in from 25 to 35 percent of patients with subacute bacterial endocarditis, and 80 percent showed some form of nephritis at autopsy. In this series only one case of renal insufficiency occurred. The occurrence of constant urinary signs in over half the patients may be explained by high fever in some and by renal infarction in others. Pulmonary emboli, although clinically not common, were observed only in patients who later died. Major cerebral emboli did not affect the prognosis in 3 out of the 4 patients who had them.

In subacute bacterial endocarditis, as in other infections, widely varying therapeutic regimens providing repeated intermittent elevations of penicillin blood levels from 2 to 10 times above the sensitivity of the organism in vitro are satisfactory for cure. The cardinal principle of treatment in this disease is to alter the dose or injection interval if the temperature does not fall within from 2 to 4 days on a particular regimen. In this series, only 2 patients survived who failed to respond within this short period to the final increase in daily dose of penicillin. Treatment was continued until clinical and laboratory signs of cure appeared. The results of treatment in this group are in accord with a cure rate of 72 percent in 817 cases collected from the literature.

An effort has been made to evaluate the effect of successfully treated subacute bacterial endocarditis on the prognosis of the underlying heart disease. Of the 7 patients who died a year or more after treatment, 2 with recurrent subacute bacterial endocarditis and the patient who died of an unrelated cause have been excluded from further consideration. Evaluation of the individual patient was difficult because each was in the age group in which death from the underlying heart disease was common, regardless of the intercession of subacute bacterial endocarditis. In spite of this difficulty in interpretation, however, the data suggest that damage from subacute bacterial endocarditis could have been involved in the death of 3 of the 4 remaining patients, all of whom died in cardiac failure.

A quarter of the patients who were successfully treated suffered one or another disability as a result of the infection. In the immediate period after treatment, cardiac failure that had not been present during the infection developed in only 2 patients in this group. Follow-up study indicated that three fourths of the patients who survived the immediate post-treatment period suffered no demonstrable ill effects from the infection. The remaining patients had some functional disability or died prematurely of causes directly related to the bacterial endocarditis. (New England J. Med., 29 June '50, R. Gorlin et al.)

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Activity of Ethyl-1-Ethanesulfonyl-4-Piperazine Hydrochloride on Traumatic Hemorrhagic Shock in the Dog: The authors used the technic of Wiggers

Ingraham, and Dilles which produced an irreversible shock following a prolonged hemorrhagic hypotension period. By extensive bleeding of the dogs while under morphine or chloralose anesthesia, the blood pressure was lowered to 40 mm. of Hg. maintained for a given time by a series of successive hemorrhages and reinjections. A total reinjection of the removed blood immediately followed the period of hypotension. The wounds were treated locally with sulfanilamide and the surviving animals were given penicillin. To minimize the seasonal or other variations which constitute the principal obstacles in this type of research, the experiments were repeated in the spring and in the autumn, and parallel experiments have been carried out in Paris and in Rome. One hundred dogs were used. The duration of hypotension was prolonged for more than the 90 minutes reported by Wiggers, and there resulted a larger proportion of irreversible shock in the control animals.

In the first series of experiments (I, II, III), 16 control dogs were subjected to 2 hours hypotension, with a mortality of 94 percent. In series IV, the control dogs exhibited a higher resistance and the period of hypotension was extended to 2-1/2 hours.

Of the different compounds tested, polyvinylpyrrolidone and tuamine (2-amino-heptane hydrochloride), did not give any protection against severe hemorrhagic shock. Two synthetic amides, the N-N-bis-diethyl-amino-ethyl-ethanesulfonamide hydrochloride (3720 R.P.) and ethyl-1-ethanesulfonyl-4-piperazine hydrochloride (3885 R.P.) gave protection.

Compound 3885 R.P. was administered to the experimental dogs at different times, either before or after the first major hemorrhage. The most favorable results were obtained when the injection of the product immediately followed the hemorrhage. The results were less constant, probably a result of rapid elimination, when the compound was injected before hemorrhage, for its effectiveness decreased rapidly during the hypotensive phase.

Among the control animals, the mortality rate was 88 percent; and 15 percent among the animals treated before or immediately after the hemorrhage. The period of survival was much longer in the protected animals than in control animals; 60 percent of the latter died within 6 hours, whereas not a single one of the treated animals died in this period.

Death from shock never occurred more than 24 hours after the hemorrhage; there was only one case of a later death in a treated animal, and this appeared to be the result of an embolism.

The untreated animals presented a clinical picture corresponding exactly with that described by Wiggers and Ingraham. Irreversible shock was constantly preceded by a marked fall of blood pressure at the end of hypotension,

and by emission of bloody feces. The treated animals practically never presented these characteristic symptoms of shock.

Concerning the mode of action of 3885 R.P., it has been previously reported that this compound cannot be classified in any known group of pharmacodynamic agents; it does not seem possible to explain the protective effect in shocked dogs by any action in the cardiovascular system in normal animals. The experiments do not exclude the possibility of a pharmacodynamic antagonism for one of the hypothetical toxic substances responsible for shock. (Proc. Soc. Exper. Biol. and Med., June '50, D. Bovet and J. Fournel)

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The Comparative Value of the Augmented Unipolar Limb Leads and the Standard Limb Leads in Myocardial Infarction: The present study was undertaken to determine the relative merit of the standard limb leads against the unipolar limb leads (augmented), in the diagnosis of myocardial infarction. Because of the advantages of unipolar electrocardiography there seems to have been a tendency recently to minimize the value of the standard limb leads. Although similar studies have been made, nevertheless it appeared to the author that the problem was sufficiently unsettled to warrant further investigation.

Twenty-five consecutive cases were selected in which there was autopsy evidence of myocardial infarction, and in which it was possible to compare the augmented unipolar limb leads with the standard limb leads. In these cases, 12 leads were available: I, II, III, aV_R, aV_L, aV_F, V_1, V_2, V_3, V_4, V_5, and V_6. Of these 25 cases, 5 had to be discarded (for the purposes of this study), because of the presence of bundle branch block. Of the remaining 20 cases, there were 8 cases of anterior myocardial infarction, 7 cases of posterior myocardial infarction, and 5 cases of both anterior and posterior myocardial infarction. Of the 13 cases of anterior infarction, there were 8 with anteroseptal infarction and 5 with anterolateral infarction. Each case was studied and the electrocardiographic data correlated with the autopsy findings.

It has been stated that Q aV_F is more significant than Q_3 because it is the source of Q_3; that is, Q_3 cannot be greater than Q aV_F, except as it is influenced by R aV_L, and so Q_3 is less specific than Q aV_F. Likewise, Q aV_L is said to be more significant than Q_1, because it is the source of Q_1. Thus Q_1 cannot be greater than Q aV_L, except as it is influenced by R aV_R, and so Q_1 is less specific than Q aV_L.

However, because, in general, Q aV_L is greater than Q_1 and because Q_3 is greater than Q aV_F, the specificity of a Q wave as determined by the above reasoning is not the only factor to be considered in the diagnosis of myocardial infarction. The usefulness of the various Q waves in diagnosis must also be

considered, even though these Q waves are influenced by R waves (R aV_R in the case of Q_1 and R aV_L in the case of Q_3). It is because Q_1 is generally smaller than Q aV_L (except in anterolateral infarction) that it is not as valuable for diagnosis as Q aV_L. By the same reasoning, because Q aV_F is generally smaller than Q_3, Q aV_F is not as valuable as Q_3 in the diagnosis of posterior infarction.

Even though the augmented unipolar limb leads are superior to the standard limb leads in theory and in the understanding of electrocardiographic mechanisms, it appears (1) that Lead III is more useful than Lead aV_F in cases of posterior infarction, and (2) that although Lead aV_L is more informative than Lead I in anteroseptal infarction (and inferior to it in anterolateral infarction), the chest leads in these cases are superior to both.

As previously mentioned, the specificity of Q waves, as determined above, is not the only factor to be considered in the diagnosis of myocardial infarction. Q aV_L may exist without anterior infarction and Q aV_F may exist without posterior infarction. Because of this, it has been found necessary to evaluate Q waves with respect to various empirical observations (this applies to both the standard and the augmented unipolar limb leads).

Although the electrical position of the heart, as determined by the unipolar limb leads, is of theoretical value and of interest, clinical usefulness in the diagnosis of myocardial infarction cannot thereby be inferred. With all the discussion of unipolar limb leads concerning heart position, and particularly specificity of Q waves, a point that seems to have been neglected is that the R waves of the unipolar limb leads which contribute to the formation of the Q waves of the standard limb leads may be more than mere passive agents. That is, the time of onset of these R waves (in aV_R and aV_L) affects very significantly the contours of the standard limb leads. The visible QRS complexes of the various leads do not all begin simultaneously in the electrocardiogram. Does not the existence of a posterior myocardial infarction influence the time of onset of R aV_L, and, by altering the instantaneous electrical axis, possibly produce a taller R aV_L than existed prior to the infarction? Thus, a deeper Q_3 than expected would result, which is not less specific, but actually more specific, than Q aV_F.

By the same reasoning, an anterior myocardial infarction could alter the path of depolarization, change the instantaneous electrical axis, change the time of onset and the contour of QRS aV_R, and consequently alter Q_1. These are not passive alterations, as frequently implied, but may actually be determining factors in the value of the various Q waves of the standard limb leads in the clinical diagnosis of myocardial infarction, augmenting their specificity. Thus, even though Q_3 is greater than Q aV_F, this does not mean lack of specificity nor more frequent false positives, but may actually mean greater specificity, in

addition to greater clinical value. Two unipolar limb leads, therefore, are not necessarily better than the standard limb lead which is their resultant.

It is, perhaps, surprising that Lead aV_L is superior to Lead I in anteroseptal infarction and inferior to Lead I in anterolateral infarction. Because Lead aV_L is the left arm lead, it might be expected to be a lateral lead rather than a septal lead. However, because of the actual position of the heart and the fact that the septum actually lies in an almost frontal plane, the septal effects are more readily projected to the left shoulder than are the lateral effects. Since the conclusion of this study it has been possible in numerous cases of anterior infarction to determine whether the lesion was anterolateral or anteroseptal by comparing Leads I and aV_L, confirmation then being had in the V leads.

Although this series is too small for decisive conclusions, it appears that the problem is still unsettled.

The author concludes that for the purpose of diagnosing any but the most unusual types of myocardial infarction, in which esophageal leads or multiple precordial leads in other than the usual 6 positions might be of help, the augmented unipolar limb leads, though helpful, do not appear necessary. As a routine procedure in the diagnosis of myocardial infarction, the standard limb leads and the precordial (unipolar) leads appear adequate and sufficient. (Am. Heart J., July '50, D. Fiske)

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The Use of Dramamine on a Naval Transport: Accumulated data support the use of dramamine in the prevention and control of motion sickness. Dramamine is not always completely effective, however, and its use has been disappointing to at least one medical officer on a naval transport whose comment in an Annual Sanitary Report is quoted:

"Dramamine was first obtained 8 months ago and has been used continuously since in rather large quantities among the cabin class passengers and troop passengers, only rarely for ships company. During the first month or two of its use on board, it seemed to be encouragingly effective in bringing relief to most sufferers of motion sickness; although the average conditions of wind, sea, and motion of the ship were calm or mild and the number of sufferers was relatively few.

Our first two departures from port in the Atlantic this winter were accompanied by a sickening pitching of the ship, heading into wind and sea. In spite of the fact that dramamine had been dispensed in suitable quantities to passengers at least 2 hours before getting underway and before the preceding meal, the incidence of motion sickness accompanied by nausea and vomiting was as bad or worse than had ever been experienced, in the memories of the transportation personnel, on this vessel.

The most often noted effect of dramamine is a profound drowsiness that demands sleep. Another effect is a sort of lightheadedness or drunkenness with disturbance of the sense of balance."

The medical officer concluded that whereas at first he had high regard for the effectiveness of dramamine, he has since, after putting it to additional test, lost faith in it. He stated that it does have a sedative effect.

Although the conclusion reached in the sanitary report quoted may not be concurred in by others, the experience on this ship will serve to discourage overconfidence in the efficacy of this drug to prevent symptoms of motion sickness. (Preventive Medicine Div., BuMed)

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Inhibition of Anaphylaxis in Guinea Pigs by D-Catechin: Because of their antagonistic activity toward preformed histamine, the use of antihistaminic agents has proved to be an effective adjunct in the treatment for various allergenic reactions. Recently, Martin et al. demonstrated in vitro the inhibitory effects of vitamin P compounds on histidine decarboxylase. This enzyme, present in animal tissues, is capable of forming histamine from histidine. Preliminary tests indicated that these vitamin P compounds are also active in vivo. Their activity might be directed toward inhibition of the formation of histamine, and thus be valuable for treatment in allergies.

In this study, 14 guinea pigs were sensitized in the manner described by Raiman et al. Half of the animals received 2 mg. of D-catechin, an aglycone flavonoid, intraperitoneally daily for 19 days. The remaining animals were not treated and served as controls. At the end of the 19-day period each animal was shocked by an intracardial injection of from 0.1 to 0.5 ml of fresh normal horse serum. The animals receiving D-catechin exhibited no anaphylactic reactions. The control animals exhibited typical reactions followed by extreme dyspnea, and finally death caused by asphyxia. The complete reaction lasted for approximately 5 minutes.

Four additional guinea pigs, that had received daily doses of D-catechin for 1 week, were injected intracardially with 0.1 mg. of histamine diphosphate. These animals died several minutes later with typical shock symptoms.

The dead control animals and the animals from the histamine group were autopsied. No significant difference in gross pathology could be observed. The predominating characteristic in both groups of animals was the constriction of the bronchiolar muscles. Each animal showed varying degrees of pulmonary edema and hyperemia.

These studies show that D-catechin protects guinea pigs from anaphylactic reactions, but not from histamine shock. It appears reasonable to believe that this protective activity might be attributed to an actual inhibition of histidine decarboxylase. This reaction would tend to prevent the formation of histamine, considered to be an important factor in the anaphylactic syndrome. (Science, 7 July '50, J. N. Moss et al.)

Training Programs for Volunteer Naval Reserve Medical Officers:

Course in Medical Aspects of Special Weapons and Radioactive Isotopes

The Commanding Officer, U. S. Naval Medical School, Bethesda, Maryland plans to conduct three courses of instruction for Volunteer Naval Reserve medical officers in Medical Aspects of Special Weapons and Radioactive Isotopes at the Naval Medical School, Bethesda, Maryland, during the fiscal year 1951. These courses are similar to those formerly conducted at the Naval Medical School. Classes are scheduled as follows:

25-30 September 1950
27 November - 2 December 1950
21-26 May 1951

Course in Aviation Medicine

It is planned to conduct two additional courses of instruction for Volunteer Naval Reserve medical officers holding the designation of flight surgeon or aviation medical examiner at the Naval School of Aviation Medicine, Pensacola, Florida, during the fiscal year 1951. Classes are scheduled as follows:

2-14 October 1950
2-14 April 1951

Course in Amphibious Medicine

It is planned to conduct two additional courses of instruction for Volunteer Naval Reserve medical officers at the Amphibious Training Command, Naval Amphibious Base, Little Creek, Virginia, during the fiscal year 1951. Classes are scheduled as follows:

2-14 October 1950
2-14 April 1951

In order to keep within the optimum age group for training in amphibious medicine it is planned to nominate only medical officers in the grade of lieutenant (junior grade) and lieutenant for this course.

The purpose of the above courses is to provide Reserve medical officers with information and technics which are not available to them in their civilian capacity, but which would be invaluable to them in the event of mobilization.

Only the 1st, 3d, 4th, 5th, 6th, 8th, and 9th Naval Districts, Potomac River Naval Command, and Chief of Naval Air Reserve Training have been assigned limited quotas for these courses. Inactive Volunteer Naval Reserve medical officers residing in these districts who desire to attend one of the above courses should submit their request for training duty to the commandant of their naval district at the earliest practicable date. Reserve medical officers who are ordered to perform active training duty in any of the above courses will be required to submit an affidavit of availability for mobilization. Requests for such active training duty, with pay, will not be approved unless the affidavit states that the individual is available within thirty days, after mobilization.

Meals and sleeping quarters will be available in the bachelor officers' quarters at the above activities for those officers who desire such accommodations. (Reserve Div., BuMed)

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American Urological Association Award: The American Urological Association announces that it is offering an annual award of $1,000.00 (first prize of $500.00, second prize $300.00, and third prize $200.00) for essays on the result of some clinical or laboratory research in urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Palmer House, Chicago, Illinois, 21 - 24 May 1951.

Those desiring full particulars should write to the Secretary, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, New Jersey. Essays must be in his hands before 10 February 1951.

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Dental Intern Program: Twenty-six dental officers have been assigned to duty under instruction in the Naval Dental Intern Program commencing 21 August. The dental intern training consists of six months of didactic and practical instruction in all phases of dentistry at the Naval Dental School, National Naval Medical Center, Bethesda, Maryland, and six months' assignment at a naval teaching hospital. (Dental Div., BuMed)

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BUMED CIRCULAR LETTER 50-68 10 July 1950

From: Chief, Bureau of Medicine and Surgery
To: All Stations within the Continental United States

Subj: Care of the Dead when Death Occurs Away from a Station Having a Contract

Ref: (a) BuMed Circular Letter No. 50-52
(b) Paragraph 341.1, Manual Medical Department, 1945
(c) Paragraph 341.6, Manual Medical Department, 1945

1. Reference (a) is hereby superseded and canceled. The material in paragraphs 2, 3, and 4 below has been brought forward from reference (a). The instructions contained in paragraph 5 have been added for clarification.

2. Reference (c) provides that "When death occurs in the continental United States away from a naval command, the dispatch forms prescribed in paragraphs 341.1 and 3418 shall be modified to conform with the circumstances. Item (j) of paragraph 341.1 shall include information as to the location of the body, the name and address of the person having custody, and, if known, the wishes of the next of kin as to disposition. The dispatch to the next of kin (par. 3418) shall be appropriate to the circumstances. Unless death has occurred at the home of the deceased, the form of dispatch to the next of kin shall be altered only by elimination of the information regarding the furnishing of the escort. Upon receipt of instructions as to disposition desired, the Bureau will arrange either through the nearest naval activity or through a local civilian undertaker for preparation and encasement of the remains at a cost not to exceed $200. with proper shipping instructions. An additional amount not to exceed $75 (par. 3447.1) may be allowed to apply to funeral expenses at final destination."

3. This Bureau has recently experienced several embarrassing situations in handling remains in cases such as those covered by reference (c). The duty stations of the individuals concerned in these particular cases contacted the nearest naval activity to the place of death and issued instructions rather than complying with reference (c). This Bureau not knowing of this action and assuming charge of the case in accordance with the regulations proceeded to issue instructions relative to preparation, encasement and disposition in accordance with reference (c). The information and instructions issued by this Bureau proved to be in conflict with action taken by the duty stations and, therefore, reflected very badly on this Bureau and the Navy Department as a whole.

4. In view of the foregoing and in order to facilitate efficient and expeditious disposition of remains in cases of this nature, it is requested that after initial instructions contained in references (b) and (c) have been complied with that no

further action be taken in order that the Bureau of Medicine and Surgery may assume charge and arrange for preparation, encasement and disposition in accordance with reference (c). In the event it is deemed necessary by the duty station to issue further instructions, the Bureau of Medicine and Surgery should be made an information addressee of the communication.

5. The foregoing instructions should not be considered as covering those cases where death occurs sufficiently close to a naval activity having a contract for care of the dead to permit that activity to assume custody of the remains for transfer to the contract undertaker for preparation and encasement. If such transfer can be accomplished, the Bureau should be informed immediately.

C. A. Swanson

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BUMED CIRCULAR LETTER 50-69 13 July 1950

From: Chief, Bureau of Medicine and Surgery
To: Commandants, 1, 3, 4, 5, 6, 8, 9, 11, 12, 13th Naval Districts and Commandant, Potomac River Naval Command

Subj: Annual Training Duty for Naval Reserve Ensign (HP) Officers During Fiscal Year 1951; Report of

Ref: (a) BuPers ltr Pers-C-1233-nd of 21 June 1950

1. It is requested that the Bureau of Medicine and Surgery be furnished a report, as of 30 September 1950, listing the names of Naval Reserve (HP) officers who performed the subject training duty authorized by reference (a).

2. This letter is cancelled upon submission of the above report. C. A. Swanson

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BUMED CIRCULAR LETTER 50-70 13 July 1950

From: Chief, Bureau of Medicine and Surgery
To: Commanding Officer, U. S. Naval Hospitals, Continental United States

Subj: Annual Training Duty for Naval Reserve Ensign (HP) Officers During Fiscal Year 1951; Information Concerning

Ref: (a) BuPers ltr Pers-C-1233-nd of 21 June 1950

Encl: (1) Copy of reference (a)

1. Enclosure (1) is forwarded herewith for information.

2. Commanding officers are encouraged to provide the Reserve Ensign (HP) officers, who may be ordered to their command for this duty, such training in the professional services as they may consider appropriate. C. A. Swanson

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BUMED CIRCULAR LETTER 50-71 13 July 1950

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Women Members of Naval Service; Physical Examinations of

Ref: (a) Par. 21110, Manual of Medical Department - Physical Examination of Officers prior to Resignation, Discharge, Dismissal, or Retirement for Age or Failure of Promotion
(b) Par. 21118, Manual of Medical Department - Physical Examination of Enlisted Men Prior to Discharge or Retirement

1. The physical examination required by references (a) and (b) shall include, in the cases of female members, examination of the external genitalia, the breasts, and a pelvic examination. The condition of the pelvic organs shall be determined by either vaginal or rectal bimanual palpation as may be appropriate. Visualization of the cervix and vaginal canal by speculum will be made in all cases except where rectal examination is required because of a nonelastic hymen. Examination of the cervix by means of a virginal-type speculum is recommended where indicated. C. A. Swanson

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BUMED CIRCULAR LETTER 50-72 (Appears in 15 July Navy Dept. Bull.)

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BUMED CIRCULAR LETTER 50-73 (Limited Distribution)

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BUMED CIRCULAR LETTER 50-74 18 July 1950

From: Chief, Bureau of Medicine and Surgery
To: All Holders of the Bulletin of Bureau of Medicine and Surgery Circular Letters

Subj: Collection of Mosquito Specimens

Ref: (a) BuMed Circ. Ltr. No. 43-124 of 3 Aug 1943

Encl: (1) Directions for Collecting, Packing, and Shipping Mosquitoes

This letter (1) cancels reference (a); (2) states that the Department of Tropical Medicine, U. S. Naval Medical School, National Naval Medical Center, Bethesda 14, Maryland is in need of adult and larval mosquito collections from Florida, Texas, Illinois, Massachusetts, Northern and Southern California, Hawaii, Caroline and Marshall Islands, Formosa, Japan, Korea, Netherlands East Indies, India, Morocco, and South America; (3) requests that thick and thin blood smears from patients with acute cases of malaria be furnished the school; and (4) contains instructions in the enclosure for the packing and shipping of specimens.

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BUMED CIRCULAR LETTER 50-75 19 July 1950

From: Chief, Bureau of Medicine and Surgery
To: All Holders of the Bulletin of Bureau of Medicine and Surgery Circular Letters

Subj: BuMed Circular Letters; Cancellation of

This letter states that the following BuMed circular letters have served their purpose and are therefore canceled: 41-61; 43-17, 102, and 139; 44-8, 12, 16, 60, 123, 126, 166, 167, 203, 209, and 263; 45-16, 68, 84, 87, 131, 134, 164, 165, 181, 188, 215, and 247; 46-5, 14, 33, 55, 71, 111, 120, 140, 143, 151, 164, 168, 173, and 177; 47-2, 3, 21, 35, 37, 45, 46, 50, 58, 61, 64, 69, 86, 88, 89, 105, 111, 121, 126, 145, 152, 154, 155, 167, 170, and 171; 48-5, 27, 33, 34, 35, 41, 44, 81, 82, 87, 89, 120, 124, 129, 138, 141, 142, and 148; 49-1, 3, 4, 20, 21, 22, 25, 36, 41, 47, 98, 111, 153, and 169.

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BUMED CIRCULAR LETTER 50-76 20 July 1950

From: Chief, Bureau of Medicine and Surgery
To: All Holders of the Bulletin of Bureau of Medicine and Surgery Circular Letters

Subj: Nonstandard Medical and Dental Material Procured; Report of

Ref: (a) BuMed Circular Letter No. 47-55

This letter cancels reference (a) and directs that certain information regarding the procurement of nonstandard items be furnished the Bureau of Medicine and Surgery periodically, in order (1) to maintain the Armed Services Catalog of Medical Materiel as an effective instrument of the Medical Department of the Navy, (2) to simplify centralized procurement, and (3) to reflect past usage experience to assist in mobilization planning.

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BUMED CIRCULAR LETTER 50-77 26 July 1950

From: Chief, Bureau of Medicine and Surgery
To: Commandants, All Naval Districts
Commandant, PRNC
Chief, Naval Air Reserve Training
Naval and Marine Corps Recruiting Services

Subj: Naval and Marine Corps Reserve Personnel Being Ordered to Extended Active Duty; Submission of Standard Form 89 (Report of Medical History) in the Cases of

Ref: (a) Paragraph 2118.5, Manual of the Medical Department

1. Reference (a) provides that U. S. Naval Reserve and U. S. Marine Corps Reserve personnel, upon being examined physically for extended active duty, shall have the results of the examination reported on Standard Form 88 (Report of Medical Examination) in triplicate, the original and one copy thereof to be forwarded to the Bureau.

2. Inasmuch as a considerable period of time may have elapsed since many of the reserve personnel were last examined physically, and in order to assist in evaluating more accurately their interval medical history, it is directed that each reserve member upon being ordered to extended active duty, whether officer or enlisted, be required to complete Standard Form 89 (Report of Medical History) in the original. This form shall then be attached to the original of Standard Form 88 and forwarded to the Bureau. C. A. Swanson

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BUMED CIRCULAR LETTER 50-78 26 July 1950

From: Chief, Bureau of Medicine and Surgery
To: All Naval Hospitals

Subj: Discharges from the Sick List of Individuals Waiting to Appear or Who Have Appeared Before a Physical Evaluation Board

Ref: (a) BUMED C/L No. 50-38 of 17 April 1950

1. The provisions of paragraph 1 of reference are amended to provide that the report outlined must be submitted by the 5th of each month instead of the 10th as formerly required.

2. This change is necessitated because of the requirement that the summary data must be completed at an earlier date. C. A. Swanson

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BUREAU OF MEDICINE AND SURGERY
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